



UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/789,051	02/26/2004	Arthur M. Krieg	C1039.70083US06	8295
<div>7590 01/18/2008</div> <div>Helen C. Lockhart, Ph.D. Wolf, Greenfield & Sacks, P.C. 600 Atlantic Avenue Boston, MA 02210</div>				
<div>EXAMINER</div> <div>OGUNBIYI, OLUWATOSIN A</div>				
<div>ART UNIT PAPER NUMBER</div> <div>1645</div>				
<div>MAIL DATE DELIVERY MODE</div> <div>01/18/2008 PAPER</div>				

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No. 10/789,051	Applicant(s) KRIEG ET AL.	
	Examiner Oluwatosin Ogunbiyi	Art Unit 1645	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 24 August 2007.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 28,31-35 and 37-47 is/are pending in the application.
- 4a) Of the above claim(s) 34,38 and 41 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 28,31-33,35,37,39,40 and 42-47 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
 Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
 Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
2. ☐ Certified copies of the priority documents have been received in Application No. _____.
3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- | | |
|---|---|
| 1) <input checked="" type="checkbox"/> Notice of References Cited (PTO-892) | 4) <input type="checkbox"/> Interview Summary (PTO-413)
Paper No(s)/Mail Date. _____ |
| 2) <input type="checkbox"/> Notice of Draftsperson's Patent Drawing Review (PTO-948) | 5) <input type="checkbox"/> Notice of Informal Patent Application |
| 3) <input checked="" type="checkbox"/> Information Disclosure Statement(s) (PTO/SB/08)
Paper No(s)/Mail Date <u>10/29/07 and 8/24/07</u> . | 6) <input type="checkbox"/> Other: _____ |

RESPONSE TO AMENDMENT

The amendment filed 8/24/07 has been entered into the record. Claims 1-27, 29-30, 36 have been cancelled. Claims 28, 31-35 and 37-47 are pending. Claims 28, 31-33, 35, 37, 39, 40 and 42-47 are under examination.

The text of Title 35 of the U.S. Code not reiterated herein can be found in the previous office action.

The information disclosure statement filed 8/24/07 and 10/29/07 has been considered. An initialed copy is enclosed.

Rejections/Objections Withdrawn

1. The objection to claim 28 is withdrawn in view of the amendment to the claim.

2. The rejection of claims 29,30 and 36 provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 28-37,38-39,40,42, 43-46 of copending Application No. 10/787,737 is withdrawn in view of the cancellation of the claims.

3. The rejection of claims 28-31,32-33,35,37,40 and 42-46 provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 41-43,44, 45, 48-50, 53, 54, 55-58, 60, of copending Application No. 11/296,644 in view of Goodchild et al. 1990 Bioconjugate Chemistry volume 1, p. 165-187 and Draper et al, 1991, WO 91/12811 is withdrawn in view of the amendment to claim 28.

4. The rejection of claims 28-33,35 and 37 provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 19-22, 32,33,35,50-53,63-64,66,81,82, 86,87,97,98, 102, 103, of copending Application No. 10/613916 in view of Goodchild et al. 1990, Bioconjugate Chemistry volume 1, p. 165-187 and Oberhauser et al. 1992 Nucleic Acids Research vol. 20 p. 533-538 and Draper et al, 1991, WO 91/12811 is withdrawn in view of the amendment to the claim 28.

5. The rejection of claims 28-33,35 and 42 provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 28-32 of copending Application No. 11/645,106 in view of Goodchild et al. 1990 Bioconjugate Chemistry volume 1, p. 165-187 and Oberhauser et al. 1992 Nucleic Acids Research vol. 20 p. 533-538 and Draper et al, 1991, WO 91/12811 is withdrawn in view of the amendment to the claim 28.

6. The rejection of claims 29-30 and 36 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement is withdrawn in view of the cancellation of the claims.

7. The rejection of claims 28, 29, 30, 37, 42, 43, 44, 45, 46 and 47 rejected under 35 U.S.C. 102(b) as being anticipated by Draper et al, 1991, WO 91/12811 as evidenced by Gura. Science vol. 270, p.575-577, 1995 is withdrawn in view of the amendment to claim 28.

8. The rejection of claims 28, 29, 30, 31, 32,37, 39, 40 (in part),42,43,44 and 45-47 rejected under 35 USC 102(e) as being anticipated by Hutcherson et al US 5,723,335 1998 (continuation of serial no 217,988, March 25, 1994) as evidenced by Gura. Science vol. 270, p.575-577, 1995 is withdrawn in view of the amendment to claim 28.

Rejections Maintained

9. The rejection of claims 28, 31-33, 35,37, 39,40, 42,43-47 provisionally rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claim 36 of copending Application No. 10/787,737 is maintained for reasons made of record in the previous office action. Applicant has elected to defer rebuttal of this rejection.

10. The rejection of claims 28, 31-33, 35, 37, 39, 40 and 42-47 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement is maintained for reasons made of record in the previous office action filed 3/22/07.

Applicants argue that the data in the specification not only establishes that CpG oligonucleotides are able to activate B cells but that they induce expression of IL-6, IL- 12 and IFN-gamma as well as stimulate NK cell activity. Applicants argue further that a conclusion that CpG ODN would not be useful in the treatment of a disease that has reduced B cells is not sufficient to support a lack of enablement and that CpG oligonucleotides produce an altered immune profile, as asserted in the specification, not just a single cell type.

Applicants' argument has been carefully considered but is not persuasive.

The instant specification has broadly defined an "immune system deficiency" to mean a disease or disorder in which the subject's immune system is not functioning in normal capacity or in which it would be useful to boost a subject's immune response for example to eliminate a tumor or cancer (e.g. tumors of the brain, lung (e.g. small cell and non-small' cell), ovary breast, prostate, colon as well as carcinomas and sarcomas) or viral (e.g. HIV, herpes), fungal (e.g. Candida sp.), bacterial or parasitic (e.g. Leishmania, Toxoplasma) infection in a subject.

Included in this broad definition of immune system deficiency also includes severe combined immunodeficiency syndrome, cell mediated immunity

deficiency syndromes, X-linked agammaglobulinaemia, antibody deficiency syndrome (see Herbet et al, The Dictionary of Immunology, page 89). Severe combined immunodeficiency is a disease in which both humoral and cell-mediated immunity is defective. In X-linked agammaglobulinaemia, there are low numbers of circulating B cells (i.e. mature) and of all immunoglobulin. Pre-B lymphocytes are present in normal numbers of the bone marrow. In this disease there is a single defect in a single gene encoding a protein tyrosine kinase. Cell mediated immunity deficiency syndromes are characterized by failure to express reactions of cell-mediated immunity (i.e. to reject an allograft, become sensitized to agents causing contact hypersensitivity, show delayed-type hypersensitivity reactions) and example include DiGeorge's syndrome, thymic hypoplasia and SCID. Antibody deficiency syndrome is characterized by low serum immunoglobulin levels and failure to produce antibody normally upon antigenic challenge. One, two or all three of the major classes of immunoglobulin (IgG, IgA and IgM) may be deficient. Antibody deficiency may exist in the presence of normal cell-mediated immunity. Types of antibody deficiencies are common variable immunodeficiency, IgA deficiency, IgG subclass deficiencies, X-linked agammaglobulinaemia and X-linked hyper-IgM syndrome (see Herbet et al, The Dictionary of Immunology, pages 10, 33, 141 and 166). Immune system deficiencies such as the primary deficiencies described above are caused by intrinsic or genetic defects in the immune system. The art does not recognize the prevention of such intrinsic or genetic defects in the immune system. However, therapeutic methods are available for primary immune system deficiencies and are geared towards immunoglobulin replacement therapy, haematopoietic stem cell transplantation (using bone marrow, cord blood or peripheral blood) and gene therapy (Cunningham et al. 2005. Nature Review Immunology vol. 5 p.880-892).

In the case of primary immune system deficiencies, there is an absence or reduced numbers of T cells or mature B cells and plasma cells (Cunningham et al). When there is an absence of T cells or mature B cells and plasma cells, said

cells are not available to be stimulated by an oligonucleotide containing an unmethylated cytosine-guanine. While it is acknowledged that the specification demonstrates the immunostimulation of other cell types such as NK cells, the specification as at the time of filing has not provided a correlation of such immunostimulatory activity with treatment or prevention of any type of immune system deficiency encompassed in the broad definition set forth above. The claims require treatment or prevention of an immune system deficiency and the specification is devoid of a correlation of the immunostimulatory activity of the instant oligonucleotide with treatment and prevention of any type of immune system deficiency.

Applicant also cites two papers Gramzinski et al (Infection and Immunity v. 69 March 2001 p. 1643-1649) and Jeamwattanaalert et al (Clinical and Vaccine Immunology, April 2007, p.342-347) to show support for treatment and prevention of parasitic infection. Applicants argue that Gramzinski describe the use of CpG ODN to prevent malaria infection in mice and that it was determined that the ability of CpG ODN to confer this protection was dependent on the ability to induce IL-12 and IFN-gamma and that the teachings of Gramzinski are consistent with the specification. Further Applicants argue that Jeamwattanaalert et al teaches a study drawn towards the immunization of mice against a malarial antigen using CpG ODN as an adjuvant and that there was long lasting protective immune response to a *Plasmodium yoelli* antigen in mice.

Applicants' argument has been carefully considered but is not persuasive.

The CpG ODN described in the Gramzinski and Jeamwattanaalert reference are not commensurate in scope with that of the instant invention. The CpG ODN of Gramzinski and Jeamwattanaalert are different sequences from the one being used in the instant invention. The CpG ODN of Gramzinski and Jeamwattanaalert is 20 base pairs in length with a particular base sequence and it is this CpG ODN that confers protection in the case of Gramzinski and acts as an adjuvant in the case of Jeamwattanaalert. The instant specification or claims does

not disclose the exact CpG ODN of these references and thus the CpG ODN are not of the same scope.

Further, the Gramzinski and Jeamwattanaalert references are drawn to prevention of mouse malaria i.e. *Plasmodium yoelli* and these references do not address the treatment and prevention of human malaria infection. It is now discovered that toll-like receptor 9 (TLR9) is the receptor for CpG ODN in vivo. The art teaches that it is difficult at best to use observations with CpG ODNs in murine studies to predict accurately the effects of TLR9 activation in humans because the cellular patterns of TLR expression vary between species so the results of TLR stimulation (in mice, for example) may not be predictive of what will occur in another (humans) (Krieg et al. Proc Am Thorac Soc vol. 4 p. 289-294, 2007, see p. 289 left column under *the role of TLR9 in the mechanism of action of CpG ODNs*).

For the medically important *Plasmodium* parasites which causes human malaria i.e. *falciparum*, *vivax*, *malariae* and *ovale*, there is currently no vaccine to prevent these types of malaria spread by the Anopheles mosquito. Infact, no vaccine exists against any human parasite (Oplinger et al. NIH Record vol. LVII, NO.9, May 6, 2005). There is no vaccine against *Plasmodium falciparum*, the deadliest of the human malaria parasites. The instant specification has not provided any correlation between immunostimulatory properties of the instant CpG ODN and the treatment and prevention of any parasitic disease.

Applicant argues that several references have examined the use of CpG vaccines in cancer model. Applicants cite Krieg (J Clin Investigation, 2007, v 117, p. 1184) and argue that Krieg describes studies including human clinical trials using CpG combination with vaccines in cancer and Sfondrini et al (FASEB 2002 vol. 16 p. 1749-1754) describes the prevention of spontaneous mammary adenocarcinoma in mice by CpG ODN.

Applicants' argument is carefully considered but is not persuasive. Sfondrini et al do not disclose the instant CpG ODN, thus the CpG ODN are not commensurate in scope. As to the Krieg reference, Krieg does not disclose the

sequence of any CpG ODN and the CpG ODN are being used as adjuvants for cancer vaccines i.e. in combination with a cancer antigen and are not administered alone. The Kataoka reference (Jpn. J. Cancer Res vol. 83 p.244-247, 1992) cited in the previous office action has long ago taught the anti-tumor activity of synthetic oligonucleotides containing cytosine-guanine in a murine tumor system. However, Krieg et al (Proc Am Thorac Soc vol. 4 p. 289-294, 2007) teaches that studies in mice do not predict accurately efficacy in vivo.

The examiner agrees that the issue of whether a drug is safe and has no side effects is not an appropriate test of enablement. The Gura et al reference was merely cited to show the state of the art as to the paucity of the use of CpG ODN in humans for the treatment or prevention of any disease or disorder due to an immune system deficiency at the time of filing of the instant invention which has priority to 1994.

The instant specification fails to provide sufficient disclosure of any unmethylated cytosine-guanine oligonucleotide in the treatment and prevention of an immune system deficiency. The specification does not predict or teach any positive therapeutic benefit correlated with an immune response generated by the administration of oligonucleotides containing an unmethylated cytosine-guanine either in a subject having any of the immune system deficiencies as defined in the specification. It is art recognized that for any novel therapy, the transition from the laboratory to the clinic (Petri dish experiments to animal experiments to bedside) is a quantum leap (Chatterjee et al. Cancer Immunol Immunother. 1994 38:75-82). Results obtained with CPG treatments under controlled conditions in mice often differ from the clinical response obtained in patients (Krieg et al. Proc Am Thorac Soc vol. 4 p. 289-294, 2007). Since the therapeutic indices of immunotherapeutic regimens can be species and model dependent it is not clear that reliance on the in vitro and in vivo stimulation of B cells with unmethylated cytosine guanine oligonucleotides accurately reflects the efficacy of the claimed therapeutic strategy or prevention strategy based upon in vitro stimulation as disclosed in the specification.

One of skill in the art could not predict the efficacy of unmethylated cytosine guanine containing oligonucleotides encompassed by the claims for the treatment and prevention of the broad scope of immune system deficiencies in a subject in view of the considerations set forth supra. Reasonable correlation must exist between the scope of the claims and the enablement set forth. In view of the absence of working examples, the nature of the invention, the state of the prior art, the unpredictability of the art and the breadth of the claims, it would require undue experimentation to practice the invention as claimed.

The specification must have been enabling at the time the invention was made and developments after the time of filing are of no consequence to what one skilled in the art would have believed at the time of filing (*In re Wright*, 27 USPQ2d 1510).

Status of Claims

Claims 28, 31-33, 35, 37, 39, 40 and 42-47 are rejected. No claims allowed.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Oluwatosin Ogunbiyi whose telephone number is 571-272-9939. The examiner can generally be reached on M-F 8:30 am - 5:00 pm. If attempts to reach the examiner by telephone are unsuccessful, the examiner's Supervisor, Shanon Foley can be reached on 571-272-0787.

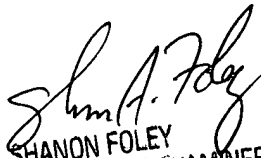
The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.



Oluwatosin Ogunbiyi

Examiner

Art Unit 1645



SHANON FOLEY
SUPERVISORY PATENT EXAMINER
TECHNOLOGY CENTER 1600